

A NOVEL SYNTHESIS OF 1,2-DEHYDRO-1-AMINO-
PHOSPHONATES VIA BECKMANN REARRANGEMENT.
APPLICATION TO THE SYNTHESIS OF α -
AMINOPHOSPHONIC ACID DERIVATIVES †

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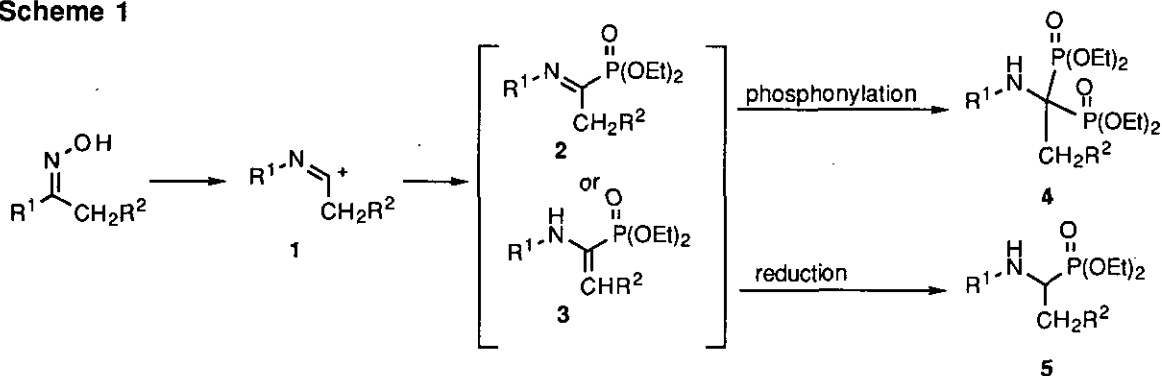
Abstract— Beckmann rearrangement of oxime mesylates (**6a,b** and **6d**) mediated by TiCl_4 in the presence of $(\text{EtO})_3\text{P}$ gave the 1,2-dehydro-1-aminophosphonates (**7a,b** and **7d**) in good yield. The utility of **7a,b** was illustrated by a synthesis of α -aminophosphonates (**11**) and (**12**).

α -Aminophosphonic acids, the phosphonic acid analogs of α -amino carboxylic acids, have received considerable attention over the past decade in medicinal chemistry owing to their potential biological activity and their unique structural features.¹ They have recently proved to be effective components for the synthesis of transition state analog inhibitors for protease.² Then, derivatives of α -aminophosphonic acids have been the focus of numerous synthetic studies. Current methodology for construction of these amino acids is available by a variety of routes.³ The reduction of 1,2-dehydro-1-aminophosphonates are also potentially useful routes for the synthesis of α -aminophosphonic acid derivatives.⁴ However, the route for the α -aminophosphonic acid derivatives *via* 1,2-dehydro-1-aminophosphonates has not been extensively studied in part due to a lack of the method of synthesis of 1,2-dehydro-1-aminophosphonic acids derivatives.⁴ In this paper, we wish to report that the Beckmann rearrangement of oxime mesylates in the

presence of phosphorus nucleophiles is applicable to a facile synthesis of cyclic 1,2-dehydro-1-aminophosphonates in good yield, in addition to the reductive transformation toward the corresponding α -aminophosphonic acid derivatives.

We have recently reported that the Beckmann rearrangement of oximes in the presence of phosphorus nucleophiles constitutes a facile synthesis of aminomethylene *gem*-diphosphonates (4) under the standard conditions (POCl_3 / CH_2Cl_2) of Beckmann rearrangement (Scheme 1).⁵ The intermediate iminocarbocations (1) were trapped efficiently with phosphorus nucleophiles to give the iminophosphonates (2), these were further phosphonylated to give aminomethylene *gem*-diphosphonate derivatives (4). In these reactions, if the phosphonylation process is able to be controlled to isolate the iminophosphonates (2) or the synthetic equivalents such as 3, the subsequent reduction of these intermediates would constitute a novel synthesis of α -aminophosphonates from oximes *via* Beckmann rearrangement.

Scheme 1

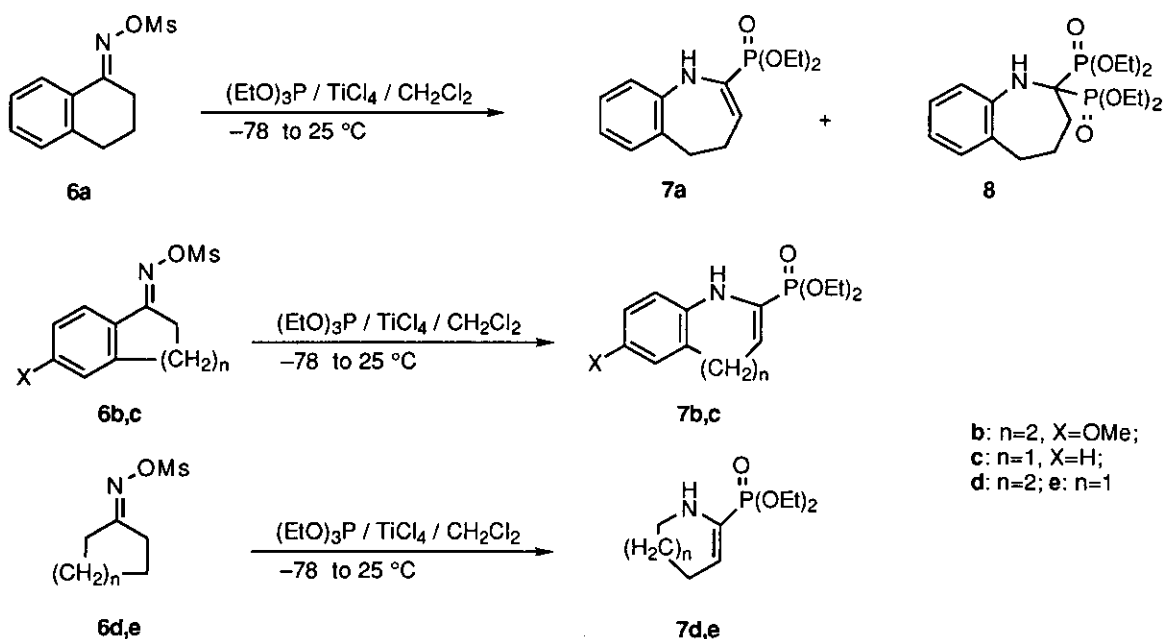


In keeping with this strategy for the synthesis of α -aminophosphonates, Lewis acid-promoted Beckmann rearrangement of oxime mesylates (6) of tetralone in the presence of phosphorus reagents was examined under a variety of conditions. Although $\text{BF}_3 \cdot \text{Et}_2\text{O}$ and Et_2AlCl did not induce the desired reaction, TiCl_4 -promoted Beckmann rearrangement of the mesylates (6) in the presence of triethyl phosphite $(\text{EtO})_3\text{P}$ was found to proceed with the desired mode (Scheme 2). Treatment of oxime mesylate (6a) with 1.2 equiv. of TiCl_4 in the presence of $(\text{EtO})_3\text{P}$ (1.2 equiv.) in CH_2Cl_2 at -78°C for 30 min, followed by warming to 25°C for 60 min, gave the corresponding 1,2-dehydro-1-aminophosphonate (7a) in 62% yield accompanied with a trace of the corresponding aminomethylene *gem*-diphosphonate derivative (8).^{5,6} The

reaction gave **7a** in virtually the same yield (60%) even in the presence of an excess of $(\text{EtO})_3\text{P}$ (3.0 equiv.). 1,2-Dehydro-1-aminophosphonate (**7a**) could be purified by chromatography on silica gel [hexane:EtOAc:Et₃N=80:10:9].

The structure of **7a** was deduced by diagnosis of doublet of triplet (δ 5.56, $J=19.4$, 4.8 Hz) attributed to the vinyl proton β to the phosphonate in ¹H nmr spectrum.

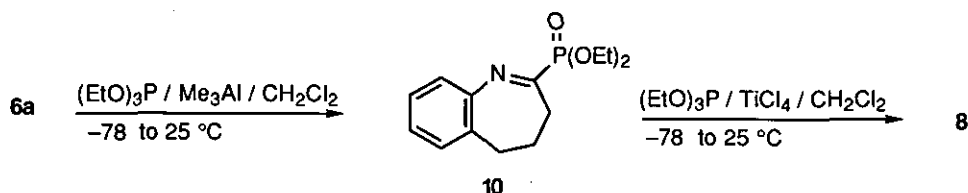
Scheme 2



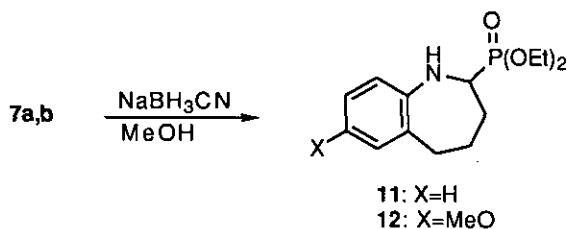
While the Beckmann rearrangement of oxime mesylates (**6c**) and (**6e**) derived from five-membered cycloalkanones such as indanone and cyclopentanone did not give the desired phosphonates (**7c**) and (**7e**), the oxime mesylates (**6b**) and (**6d**) of six-membered cycloalkanones gave the corresponding 1,2-dehydro-1-aminophosphonates (**7b**)⁶ and (**7d**)⁶ in 55 and 51% yields, respectively, under the same conditions as above.

Formation of **7** might not involve the isomerization of the corresponding iminophosphonates. Because the iminophosphonate (**10**),⁷ prepared in low yield (20%) by trimethylaluminum (Me_3Al) catalyzed Beckmann rearrangement of **6a** in the presence of $(\text{EtO})_3\text{P}$,⁸ gave the aminomethylene *gem*-diphosphonate (**8**)⁵ without formation of **7a** upon treatment with $(\text{EtO})_3\text{P}$ in the presence of TiCl_4 . A clear understanding of the

formation of **7** in TiCl_4 -mediated Beckmann rearrangement of oxime mesylate in the presence of $(\text{EtO})_3\text{P}$ must await further experimentation.



1,2-Dehydro-1-aminophosphonates (**7a,b**) thus obtained gave the corresponding α -aminophosphonates (**11**) and (**12**) as oils in good yields [**11**: 84%; **12**: 73%],⁶ upon treatment with NaBH_3CN in MeOH containing 2N HCl .^{9,10} Thus, TiCl_4 -catalyzed Beckmann rearrangement of oxime mesylate in the presence of phosphorus reagent constitutes a facile synthesis of α -aminophosphonates *via* reduction of 1,2-dehydro-1-aminophosphonates.



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REFERENCES AND NOTES

- ¶ Dedicated to professor Shigeru Oae on the occasion of his 77th birthday.
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 3. V. P. Kukhar, V. A. Soloshonok, and V. A. Solodenko, *Phosphorus, Sulfur and Silicon*, 1994, **92**, 239; H. Sasai, S. Arai, Y. Tahara, and M. Shibasaki, *J. Org. Chem.*, 1995, **60**, 6656; A. B. Smith III, K. M. Yager, and C. M. Taylor, *J. Am. Chem. Soc.*, 1995, **117**, 10879 and references cited therein.

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5. T. Yokomatsu, Y. Yoshida, N. Nakabayashi, and S. Shibuya, *J. Org. Chem.*, 1994, **59**, 7562.
6. All new compounds except unstable oils provided satisfactory analytical and spectroscopic data.
Spectroscopic data of selected new compounds: **7a**: an oil; ^1H nmr (300 MHz, CDCl_3) δ 7.09-7.01 (2H, m), 6.85 (1H, dd, $J=7.1, 7.5$ Hz), 6.75 (1H, d, $J=7.5$ Hz), 5.88 (1H, d, $J=11.8$ Hz), 5.56 (1H, dt, $J=19.4, 4.8$ Hz), 4.20-4.03 (4H, m), 3.02-2.94 (2H, m), 2.63-2.54 (2H, m), 1.40-1.32 (6H, m); ^{13}C nmr (100 MHz, CDCl_3) δ 143.96 (d, $J=13$ Hz), 131.37, 130.42, 128.48, 126.68, 121.43, 118.70, 115.18 (d, $J=12.9$ Hz), 62.50 (d, $J=4.5$ Hz), 34.20, 29.77 (d, $J=16.7$ Hz), 16.25 (d, $J=6.1$ Hz); ^{31}P nmr (160 MHz, CDCl_3) δ 17.0; ir (neat) 1258, 1235, 1055, 1024 cm^{-1} ; ms(EI) m/z 281 (M^+); HRms m/z calcd for $\text{C}_{14}\text{H}_{20}\text{NO}_3\text{P}$: 281.1181, Found: 281.1208. **7b**: an unstable oil; ^1H nmr (300 MHz, CDCl_3) δ 6.75-6.6 (3H, m), 5.67 (1H, d, $J=11.7$ Hz), 5.48 (1H, dt, $J=19.0, 5.7$ Hz), 4.20-4.05 (4H, m), 3.76 (3H, s), 2.98-2.92 (2H, m), 2.61-2.54 (2H, m), 1.42-1.31 (6H, m); ^{31}P nmr (160 MHz, CDCl_3) δ 16.6; ir (neat) 1257, 1234, 1054, 1023 cm^{-1} ; ms(EI) m/z 295 (M^+). **7d**: an unstable oil, ^1H nmr (300 MHz, CDCl_3) δ 5.66 (1H, dt, $J=11.4, 5.83$ Hz), 4.20-4.0 (4H, m), 3.85-3.81 (1H, m), 2.39-2.18 (2H, m), 1.75-1.30 (4H, m), 1.38-1.29 (6H, m); ms(EI) m/z 233 (M^+); HRms m/z calcd for $\text{C}_{10}\text{H}_{20}\text{NO}_3\text{P}$: 233.1181, Found: 233.1171. **11**: an oil; ^1H nmr (300 MHz, CDCl_3) δ 7.10 (1H, d, $J=6.93$ Hz), 7.05 (1H, dd, $J=7.1, 1.5$ Hz), 6.89 (1H, dd, $J=7.1, 7.5$ Hz), 6.85 (1H, d, $J=7.5$ Hz), 4.20-4.10 (4H, m), 3.13 (1H, ddd, $J=16.1, 11.0, 2.1$ Hz), 2.83-2.64 (2H, m), 2.28-2.15 (1H, m), 2.14-1.98 (1H, m), 1.89-1.75 (1H, m), 1.48-1.32 (7H, m); ^{13}C nmr (100 MHz, CDCl_3) δ 148.21 (d, $J=12$ Hz), 133.85, 130.55, 126.81, 121.89, 120.28, 62.53 (d, $J=6.3$ Hz), 62.30 (d, $J=6.6$ Hz), 55.50 (d, $J=144.5$ Hz), 35.28, 31.32, 26.36 (d, $J=16.6$ Hz), 16.5 (br s); ^{31}P nmr (160 MHz, CDCl_3) δ 27.2; ir (neat) 3329, 1481, 1258, 1228, 1053, 1024 cm^{-1} ; ms m/z 283 (M^+); HRms m/z calcd for $\text{C}_{14}\text{H}_{22}\text{NO}_3\text{P}$: 283.1337, Found: 283.1342. **12**: an oil; ^1H nmr (300 MHz, CDCl_3) δ 6.81 (1H, d, $J=8.3$ Hz), 6.68 (1H, d, $J=2.8$ Hz), 6.61 (1H, dd, $J=8.3, 2.8$ Hz), 4.20-4.10 (4H, m), 3.76 (3H, s), 3.05 (1H, ddd, $J=16.2, 11.0, 2.1$ Hz), 3.39-3.22 (2H, m), 2.25-2.15 (1H, m), 2.09-2.0 (1H, m), 1.90-1.75 (1H, m), 1.39-1.30 (7H, m); ^{13}C nmr (100 MHz, CDCl_3) δ 142.50 (d, $J=12.0$ Hz), 136.05, 121.48, 116.16, 111.48, 62.51 (d, $J=5.9$ Hz), 62.31 (d, $J=6.7$ Hz), 55.97 (d, $J=144.2$

Hz), 55.31, 35.42, 31.57, 26.50 (d, $J=16.6$ Hz), 16.55 (br s); ^{31}P nmr (160 MHz, CDCl_3) δ 27.4; ir (neat) 3329, 1505, 1257, 1227, 1051, 1024 cm^{-1} ; ms(EI) m/z 287 (M^+).

7. Since **10** was difficult to isolate as a pure state due to its instability toward silica gel column chromatography, the structure and yield of **10** were determined after reduction [NaBH_4 / MeOH] to α -aminophosphonate (**11**).
8. The competitive methylation of iminocarbocation was the major reaction as reported by Yamamoto: K. Maruoka, T. Miyazaki, M. Ando, Y. Matsumura, S. Sakane, K. Hattori, and H. Yamamoto, *J. Am. Chem. Soc.*, 1983, **105**, 2831; Y. Matsumura, J. Fujiwara, K. Maruoka, and H. Yamamoto, *J. Am. Chem. Soc.*, 1983, **105**, 6312.
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10. 1,2-Dehydro-1-aminophosphonates (**7**) were inert to NaBH_4 -reduction in MeOH. The results also support the structure of **7**.

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